# The influence of acute pulmonary hypertension on cardiac output measurements : calibrated pulse contour analysis, transpulmonary and pulmonary artery thermodilution against a modified fick method in an animal model

Kutter, Annette P N ; Mosing, Martina ; Hartnack, Sonja ; Raszplewicz, Joanna ; Renggli, Martina ; Mauch, Jacqueline Y ; Hofer, Christoph K

Abstract: BACKGROUND: In critically ill patients with significant pulmonary hypertension (PH), close perioperative cardiovascular monitoring is mandatory, considering the increased morbidity and mortality in this patient group. Although the pulmonary artery catheter is still the standard for the diagnosis of PH, its use to monitor cardiac output (CO) in patients with PH is decreasing as a result of increased morbidity and possible influence of tricuspid regurgitation on the measurements. However, continuous CO measurement methods have never been evaluated under PH regarding their agreement and trending ability. In this study, we evaluated the influence of acute PH and different CO states on transpulmonary thermodilution (TPTD) and calibrated pulse contour analysis (PiCCO; both assessed with PiCCO plus(TM)), intermittent pulmonary artery thermodilution (PATD), and continuous thermodilution (CCO) compared with a modified Fick method (FICK) in an animal model. METHODS: Nine healthy pigs were studied under anesthesia. PH of 25 and 40 mm Hg (by administration of the thromboxane analog U46619), CO decreases, and CO increases were induced to test the different CO measurement techniques over a broad range of hemodynamic situations. Before each step, a new baseline data set was collected. CO values were compared using Bland-Altman analysis; trending abilities were assessed via concordance and polar plot analysis. The influence of pulmonary pressure on CO measurements was analyzed using linear mixed models. RESULTS: A mean bias of -0.26 L/min with prediction intervals of -0.88 to 1.4 L/min was measured between TPTD and FICK. Their concordance rate was 100% (94%-100% confidence interval), and the mean polar angle -3[degrees] with radial limits of agreement of +/-28[degrees] indicated good trending abilities. PATD compared with FICK also showed good trending ability. Comparisons of PiCCO and CCO versus FICK revealed low agreement and poor trending results with concordance rates of 84% (71%-93%) and 88% (74%-95%), mean polar angles from -17[degrees] and -19[degrees], and radial limits of agreement of +/-45[degrees] and 40[degrees]. Pulmonary pressures influenced only the difference between FICK and PiCCO, as assessed by linear mixed models. CONCLUSIONS: TPTD compared with FICK was able to track all changes induced during the study period, including those by PH. It yielded better agreement than PATD both compared with FICK. PiCCO and CCO were not mapping all changes correctly, and when used clinically in unstable patients, regular controls with intermittent techniques are required. Acute pharmacologically induced PH did influence the difference between FICK and PiCCO.

DOI: https://doi.org/10.1213/ANE.0000000000000655

Originally published at:
Kutter, Annette P N; Mosing, Martina; Hartnack, Sonja; Raszplewicz, Joanna; Renggli, Martina; Mauch, Jacqueline Y; Hofer, Christoph K (2015). The influence of acute pulmonary hypertension on cardiac output measurements : calibrated pulse contour analysis, transpulmonary and pulmonary artery thermodilution against a modified fick method in an animal model. Anesthesia and Analgesia, 121(1):99-107.
DOI: https://doi.org/10.1213/ANE.0000000000000655

**Anesthesia and Analgesia, in press**

# Influence of acute pulmonary hypertension on cardiac output measurements: Calibrated pulse contour analysis, transpulmonary and pulmonary artery thermodilution against a modified Fick method in an animal model

A P N Kutter[1], M Mosing[1], S Hartnack[2], J Raszplewicz[1], M Renggli[1], J Y Mauch[3], C K Hofer[4]

[1]Section of Anesthesiology, Equine Department,
Vetsuisse Faculty of the University of Zurich, Zurich, Switzerland

[2]Section of Epidemiology, Vetsuisse Faculty of the University of Zurich,

[3]Department of Anesthesiology, Kantonsspital Luzern, Luzern, Switzerland

[4]Institute of Anesthesiology and Intensive Care Medicine, Triemli City Hospital, Zurich, Switzerland

**Corresponding Author:**
Annette P N Kutter
Section of Anesthesiology, Equine Department,
Vetsuisse Faculty of the University of Zurich,
Winterthurerstrasse 260, 8057 Zurich, Switzerland
Phone: +41 6358488
Fax: +41 6358905
Email: akutter@vetclinics.uzh.ch

**Abstract**

**Background**

In critically ill patients with significant pulmonary hypertension (PH) close perioperative cardiovascular monitoring is mandatory, considering increased morbidity and mortality in this patient group. Although the pulmonary artery catheter is still the standard for the diagnosis of PH, its use to monitor cardiac output (CO) in PH patients is decreasing as a result of increased morbidity and possible influence of tricuspid regurgitation on the measurements. However, continuous CO measurement methods have never been evaluated under PH regarding their agreement and trending ability. The aim of this study was to evaluate the influence of acute PH and different CO states on transpulmonary thermodilution (TPTD) and calibrated pulse contour analysis (PiCCO; both assessed with PiCCOplus$^{TM}$), intermittent (PATD) and continuous (CCO) pulmonary artery thermodilution as compared to a modified Fick method (FICK) in an animal model.

**Methods** Nine healthy pigs were studied under anesthesia. Pulmonary hypertension of 25 and 40 mmHg (by administration of the thromboxane analogue U46619), CO de- and increases were induced to test the different CO measurement techniques over a broad range of hemodynamic situations. Before each step a new baseline data set was collected. CO values were compared using Bland-Altman analysis; trending abilities were assessed using concordance and polar plot analysis. The influence of pulmonary pressure on CO measurements was analyzed using linear mixed models.

**Results** A mean bias of -0.26 L/min with prediction intervals of -0.88 to 1.4 L/min were measured between TPTD and FICK. Their concordance rate was 100% (94-100%)(confidence interval) and the mean polar angle -3° with radial limits of agreement (RLOA) of ± 28° indicated good trending abilities. PATD compared to FICK also showed good trending ability. Comparisons of PICCO and CCO vs. FICK revealed low agreement and poor trending results with concordance rates of 84% (71-93%) and 88% (74-95%); mean polar angles from -17° and -19° and RLOA of ± 45° and 40°. Pulmonary pressures influenced only the difference between FICK and PiCCO, as assessed by linear mixed models.

***Conclusion***

TPTD compared to FICK was able to track all changes induced during the study period including those by PH. It yielded better agreement than PATD both compared to FICK. PiCCO and CCO were not mapping all changes correctly and when used clinically in unstable patients, regular controls with intermittent techniques are required. Acute pharmacologically induced PH did influence the difference between FICK and PiCCO.

## Introduction

Patients with pulmonary hypertension (PH) have an increased morbidity and mortality in the perioperative setting of both cardiac and non-cardiac surgery.[1-3] Although close monitoring of cardiovascular function is mandatory in patients with PH[4] the perioperative use of the pulmonary artery catheter has been questioned as a result of an increased risk of arrhythmias and vessel ruptures in this patient group.[5, 6] Furthermore, pulmonary artery thermodilution (PATD) cardiac output (CO) measurements may be distorted by tricuspid regurgitation.[7] The severity of PH does not predict mortality, but measuring CO repeatedly and assessing the function of the right heart is an important prognostic factor and a measure of therapeutic success.[4]

Transpulmonary thermodilution (TPTD) may be a valuable alternative to PATD for CO measurements in the setting of PH and may overcome some problems related to PATD in PH. Using TPTD the PATD catheter is replaced typically by a femoral or long radial artery thermodilution catheter.[8] A cold fluid bolus is injected in the jugular vein or the right atrium by means of a central venous catheter. The temperature change following cold fluid administration is not detected in the pulmonary artery, but only after the fluid bolus has passed both sides of the heart and the lung in the central systemic circulation. Therefore, this CO measurement method is called “transpulmonary”. It is used in the PiCCOplus monitoring system to calibrate the continuous pulse contour analysis (PiCCO). Thus, this system can be used at the bedside to assess CO.

However, TPTD and PiCCO have never been compared to a reference technique under increased pulmonary pressure conditions and their accuracy and trending ability in this setting is not known. Differences between methods can be induced through bias, different variability or different susceptibility to extraneous factors[9] like changes of systemic or pulmonary arterial pressures. For clinical CO monitoring however, the accurate mapping of changes over time may be more important than the absolute CO value per se, in order to detect hemodynamic instability or to assess results of therapeutic measures.[10, 11]

Continuous pulmonary artery thermodilution (CCO) measures CO with a modified pulmonary artery catheter equipped with a thermal coil, which is positioned in the right ventricle. The coil generates heat pulses and by repeatedly doing so the CO computer can construct a thermodilution washout curve and estimate CO automatically. The method has been evaluated in many studies with good agreement for slow hemodynamic changes, but during fast changes a time delay from 5 to 20 minutes to track changes has been reported.[12]

The aim of this study evaluate the influence of acute PH and different CO states on CO measurements by TPTD, PiCCO, PATD and CCO as compared to a modified Fick method (FICK) in an animal model. The hypothesis was, that changes in lung perfusion would influence TPTD and PiCCO less than PATD and continuous CO assessment by thermodilution (CCO) using the pulmonary artery catheter.

## Methods

### General

This study was approved by the Cantonal Veterinary Office of Zurich (176/2011). Nine healthy landrace pigs aged 62 ± 1 day (mean ± standard deviation (SD)), weighing 25.7 ± 1.9 kg were studied. The sample size of ten pigs was chosen on the basis of previous studies investigating agreement between CO methods in animal models.[13,14] Only 9 pigs were included in the current study due to missing FICK CO data in one pig.

The pigs were premedicated with midazolam 1 mg/kg (Dormicum, Roche Pharma, Switzerland) and ketamine 15 mg/kg (Narketan, Vetoquinol, Switzerland) intramuscularly. Anesthesia was induced with propofol (Propofol, Fresenius Kabi, Switzerland) and maintained with midazolam 0.5 mg/kg/h, propofol 4 mg/kg/h, fentanyl 20 µg/kg/h (Sintenyl, Sintetica SA, Switzerland) and pancuronium 0.2 mg/kg/h (Pavulon, Essex Chemie AG, Switzerland). Ringers lactate solution at a rate of 3 mL/kg/h (Ringer Laktat, Fresenius Kabi, Switzerland) was infused during the experiment and temperature was kept constant at 38.5 ± 0.3°C by means of a forced-air warming blanket (Bair Hugger, Carbamed AG, Liebefeld, Switzerland).

After endotracheal intubation the pigs were placed in dorsal recumbency and mechanical ventilation (S/5 Advance Anesthesia Machine, Datex-Ohmeda Inc., Madison, WI) was started using a volume controlled mode with the following settings: tidal volume of 6 mL/kg, positive end-expiratory pressure level of 7 $cmH_2O$, inspiratory-to-expiratory ratio of 1:1 and $FiO_2$ of 0.5. Respiratory rate was adjusted to keep the end-tidal partial pressure of $CO_2$ at 40 ± 3 mmHg.

### Instrumentation

A 20 G catheter was placed in the carotid artery for blood gas sampling. A 7.5 Fr CCO pulmonary artery catheter (Swan-Ganz TD Catheter®, Edwards Lifesciences AG, Switzerland) was placed via an 8.5 Fr introducer in the right internal jugular vein using

pressure guidance. A 4 Fr (22 cm) thermistor tipped femoral artery catheter (Pulsiocath PVPK2014L22-A, Pulsion Medical Systems, Munich, Germany) was introduced into the right femoral artery. An additional catheter was placed in the right atrium via the right jugular vein for administration of U46619. All catheters were inserted by means of a surgical cut-down. Standard three-lead electrocardiography, pulse oximetry, blood temperature, right atrial, pulmonary and peripheral arterial pressures were displayed using a multiparameter monitor (GE BL850, Anandic Medical Systems AG, Switzerland). Bispectral index (Bispectral Index Monitor, Model A-2000, Aspect Medical System, Inc., Newton, MA) was applied for monitoring and adjustment of depth of anesthesia in pigs as described before.[15] Expired $CO_2$ analysis was performed with a mainstream $CO_2$ infrared analyzer (NICO2, Respironics Inc., Murrysville, Pennsylvania). Mixed venous and arterial blood samples were taken before each CO measurement and blood gases as well as hemoglobin were immediately measured using a co-oximeter (GEM 4000, IL, Axon Lab, Switzerland).

**Cardiac Output Measurements**

To assess CO with a modified Fick method (FICK), the $CO_2$ production per minute was calculated from the area under the curve of the capnogram during in- and expiration multiplied with the respiratory rate.[16] The $CO_2$ production was divided by a respiratory quotient of 0.8 to receive $O_2$ consumption. This value was divided by the arterio-venous $O_2$ content difference to receive FICK CO values. Fick measurement was chosen as the reference method to exclude a potential influence of PH or tricuspid regurgitation that is reported for thermodilution methods.

Each intermittent thermodilution measurement consisted of four fluid boluses of 10 mL ice-cold 5% dextrose manually injected by the same operator into the proximal port of the pulmonary artery catheter located in the right atrium. Fluid bolus temperature was detected by two serial in-line sensors of the two cardiac output computers (PATD: Vigilance I, Edwards Lifesciences AG, Switzerland and TPTD: PiCCO Plus™, software version 6.0, Pulsion Medical Systems, Munich, Germany). The temperature changes in the pulmonary artery and in the distal abdominal aorta were simultaneously recorded with the two thermistor-tipped catheters and CO was calculated based on the Stewart-Hamilton equation by the corresponding CO computer. All thermodilution curves were visually controlled for regular shape. The mean of three thermodilution measurements within a variation of 10% was used to

calculate $PATD_{mean}$ and the 3 corresponding TPTD to calculate $TPTD_{mean}$, which were used for statistical analysis.

The PiCCOplus monitor automatically calibrates the pulse contour measurement PiCCO after every new set of TPTD bolus measurements. This calibration was allowed at each baseline measurement. During the step measurement, the automatic recalibration was not allowed. To prevent this calibration, the TPTD bolus measurements obtained during the steps were manually deleted in the monitors' memory. This enabled us to analyze the trending ability over each intervention step ($PH_{25}$, $PH_{40}$, $CO_{up}$ and $CO_{down}$) over a one-hour period.

In order to avoid influence of the cold injectate, continuous PiCCO and CCO values were recorded directly before a new set of bolus measurements was performed. Pulmonary artery wedge pressures were measured after CO measurements by occluding the pulmonary artery with the balloon on the tip of the pulmonary artery catheter. If the artery could not be occluded during the step $PH_{25}$ or $PH_{40}$ due to dilation of the vessel, no repositioning of the catheter was attempted to avoid interference with concurrent dead space measurements performed for another study in the same pigs.[14] We report the global ejection fraction (GEF) as it is calculated by the PiCCOplus monitor: GEF [mL] = stroke volume / (GEDV / 4). GEDV is assessed from the transpulmonary thermodilution curve: CO * (mean transit time – exponential downslope time). GEDV and GEF assessments have been described in detail.[17]

*Study protocol*

In order to assess the influence of changes of pulmonary and systemic pressures and the performance of different cardiac output measurement methods four individual steps were defined (**Figure 1**). Two levels of pulmonary hypertension - i.e. $PH_{25}$ (mean pulmonary artery pressure of 25 mmHg) and $PH_{40}$ (mean pulmonary artery pressure of 40 mmHg) - were induced by infusing 2 µg/kg/min U46619, a thromboxane analogue, into the right atrium. The rate was increased or decreased in order to reach a stable target pressure of either a mean pulmonary artery pressure of 25 mmHg or 40 mmHg. To increase pulmonary pressures by rising lung perfusion CO was increased by 50% from baseline ($CO_{up}$) by administration of 30 mL/kg Ringers lactate and dobutamine (Dobutrex, Teva Pharma AG, Switzerland) at an initial dose of 5 µg/kg/min. The dose of dobutamine was adapted in order to reach the target CO value. CO was decreased by 40% from baseline ($CO_{down}$) by sodium nitroglycerine infusion 30 µg/kg/min (Perlinganit, UCB Pharma AG, Switzerland) and esmolol 500 µg/kg/min (Esmolol OrPha Swiss GmbH, Switzerland). All steps were performed in random order in an

individual pig. Baseline data were obtained before each protocol step. CO measurements were started after reaching stable conditions for 5 minutes of the predefined pressure or CO values. At least 30 minutes were allowed between steps and the next step was initiated when cardiovascular parameters were within 5% of the baseline values. At the completion of the experiment the pigs were sacrificed by intravenous administration of pentobarbital (Esconarkon, Streuli AG, Switzerland).

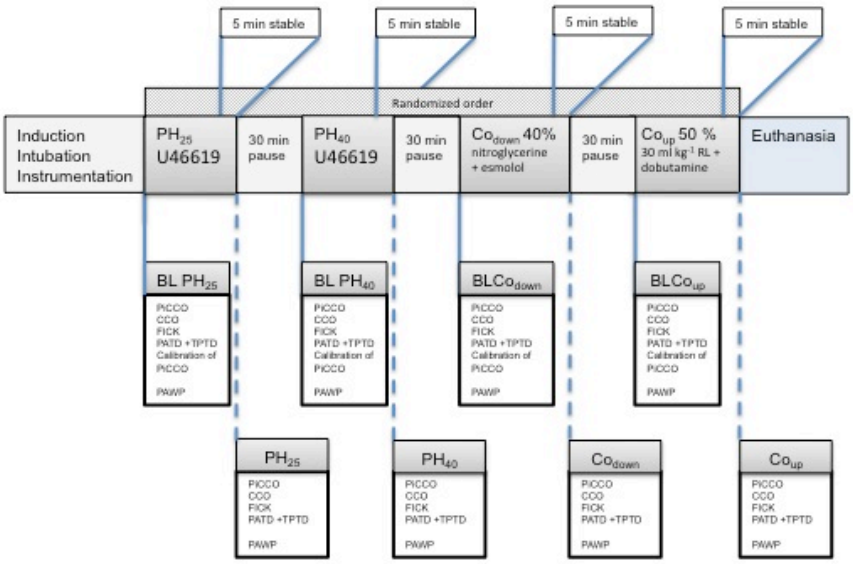



**Figure 1 Study protocol**
$PH_{25}$ and $PH_{40}$: pulmonary hypertension 25 mmHg and 40 mmHg, $CO_{down}$: cardiac output decrease and $CO_{up}$: increase; RL: Ringer's Lactate solution, U 46619: thromboxane analogue, FICK: modified Fick method, PiCCO: pulse contour analysis with PiCCOplus$^{TM}$, CCO: continuous thermodilution, PATD: pulmonary artery and TPTD: transpulmonary thermodilution, PAWP: pulmonary artery wedge pressure

*Statistical analysis*

Cardiovascular changes were analyzed by paired t-tests. Comparison of absolute CO values measured by the different techniques was performed by linear mixed effects models and by Bland-Altman analysis. To adjust for the small sample size the t-statistic for 9 pigs was calculated: $t_{0.975}^{(9-1)} \times \sqrt{1 + 1/9} = 2.431$. To calculate the prediction intervals (limits of agreement) 2.431 was multiplied with the SD of the mean bias. The commonly used value of 1.96 can be used in studies with n ≥ 60. Mean percentage error was calculated as 100 x 2.431 x SD of the mean bias / mean CO of both methods to make the results comparable to former studies and between steps.[18]

For the comparison of trending capabilities of the different techniques changes of CO (Δ CO) were calculated for each set of measurements and concordance and polar plots were done as

recently described by Critchley et al.,[10, 11] setting the exclusion zone at CO changes of ≤ 10% (polar plot) and ≤15% (concordance). To calculate the confidence interval (CI) of the concordance rate generalized mixed effects models with pig as random effect and an intercept were fitted. The exponential of the beta coefficient of the intercept (± 2 x standard error) corresponds to the odds (95% CI of odds). The odds -being equal to π/1- π- were solved for π (and the corresponding lower and upper limits).

Linear mixed effects models were also used to assess if a potential association between mean arterial or mean pulmonary artery blood pressure and the measured CO values was influenced by the method (interaction effect between method and mean arterial or mean pulmonary artery blood pressure). Utilizing the triplicate measurements, linear mixed effects models were applied to test the difference of the variability of PATD and TPTD. Model selection (e.g. deciding which of the explanatory variables - mean arterial blood pressure, mean pulmonary artery blood pressure, effect of CO method or an interaction term - should be included in the final model) was based on Akaike information criteria, which is a goodness-of-fit criterion model that allows a qualitative assessment of the variables with lower values indicating a better model fit.[19] Data management was done using Excel for Macintosh (Office X, Microsoft, Redmond, WA). Graphs were performed with Prism 6.0f (GraphPad Software, San Diego,CA) and SigmaPlot 10.0 (Systat Software, San Jose, CA). Linear mixed models and Bland-Altman calculations with repeated measures were performed with R[20] and the packages nlme[21] and MethComp.[22]

## Results

Hemodynamic data during the study period are displayed in **Table 1**. All techniques (FICK, PATD, CCO, TPTD, PiCCO) detected the significant CO reduction (all $p < 0.039$) and CO increase (all $p < 0.016$) during step $CO_{down}$ and $CO_{up}$, respectively. Drug induced pulmonary hypertension of 25 mmHg did not result in significant changes in CO assessed by any of the used methods (all $p > 0.134$), while PH 40 mmHg induced a significant decrease in CO in all methods (all $p < 0.025$) but CCO ($p = 0.236$).

**Table 1. Hemodynamic changes during the study period**

| | $PH_{25}$ | | $PH_{40}$ | | $CO_{down}$ | | $CO_{up}$ | |
|---|---|---|---|---|---|---|---|---|
| | **BL** | **Step** | **BL** | **Step** | **BL** | **Step** | **BL** | **Step** |
| **FICK** | 3.7 | 3.7 | 4.1 | ★3.2 | 3.9 | ★2.3 | 3.7 | ★6.7 |
| (L/min) | ±0.5 | ±0.6 | ±0.9 | ±0.5 | ±0.6 | ±0.3 | ±0.5 | ±0.8 |
| | | p = 0.67 | | p = 0.002 | | p < 0.0001 | | p < 0.0001 |
| **PATD** | 3.2 | 3.0 | 3.4 | ★2.8 | 3.1 | ★1.9 | 3.1 | ★5.5 |
| (L/min) | ±0.5 | ±0.3 | ±0.6 | ±0.3 | ±0.5 | ±0.5 | ±0.5 | ±0.7 |
| | | p = 0.14 | | p = 0.001 | | p = 0.001 | | p < 0.0001 |
| **TPTD** | 3.6 | 3.5 | 3.8 | ★3.1 | 3.5 | ★2.4 | 3.5 | ★5.7 |
| (L/min) | ±0.5 | ±0.5 | ±0.5 | ±0.4 | ±0.5 | ±0.2 | ±0.4 | ±0.7 |
| | | p = 0.61 | | p = 0.0004 | | p = 0.0001 | | p < 0.0001 |
| **PiCCO** | 3.7 | 3.3 | 3.8 | ★3.3 | 3.6 | ★2.8 | 3.6 | ★4.3 |
| (L/min) | ±0.6 | ±0.6 | ±0.7 | ±0.4 | ±0.6 | ±0.6 | ±0.5 | ±0.6 |
| | | p = 0.13 | | p = 0.025 | | p = 0.04 | | p = 0.02 |
| **CCO** | 4.5 | 4.3 | 4.5 | 4.3 | 4.2 | ★3.4 | 4.1 | ★5.1 |
| (L/min) | ±1.1 | ±0.8 | ±1.1 | 0.9 | ±0.9 | ±0.9 | ±0.9 | ±0.8 |
| | | p = 0.29 | | p = 0.24 | | p = 0.0007 | | p =0.007 |
| **HR** | 106 | 103 | 113 | 114 | 107 | 108 | 111 | 120 |
| (1/min) | ±6 | ±7 | ±9 | ±11 | ±6 | ±15 | ±10 | ±14 |
| **MAP** | 79 | ★87 | 80 | 87 | 80 | ★33 | 77 | ★112 |
| **(**mmHg) | ±10 | ±11 | ±11 | ±13 | ±10 | ±5 | ±11 | ±14 |
| | | p = 0.002 | | p = 0.15 | | p < 0.0001 | | p < 0.0001 |
| **CVP** | 5 | 6 | 5 | ★7 | 6 | 5 | 6 | ★8 |
| (mmHg) | ±2 | ±3 | ±2 | ±1 | ±2 | ±2 | ±2 | ±2 |
| | | p = 0.1 | | p = 0.0002 | | p = 0.1 | | p = 0.007 |
| **SVR** | 1590 | ★1777 | 1497 | ★2097 | 1581 | ★971 | 1558 | ★1248 |
| (dyn•sec/$cm^5$) | ±240 | ±314 | ±308 | ±558 | ±303 | ±200 | ±260 | ±144 |
| | | p = 0.02 | | p = 0.001 | | p = 0.0008 | | p = 0.002 |
| **MPAP** | 17 | ★25 | 17 | ★41 | 17 | ★14 | 17 | ★21 |
| (mmHg) | ±1 | ±1 | ±2 | ±3 | ±1 | ±2 | ±1 | ±2 |
| | | p < 0.0001 | | p < 0.0001 | | p = 0.0002 | | p = 0.0001 |
| **PAWP** | 5 | 5 | 6 | 6 | 6 | 6 | 6 | ★7 |
| (mmHg) | ±1 | ±0.7 | ±1 | (n=1) | ±1 | ±2 | ±1 | ±2 |
| | | p = 0.6 | | | | p = 0.27 | | p = 0.03 |
| **GEF** | 34 | ★31 | 34 | ★26 | 33 | ★24 | 33 | ★42 |
| (%) | ±3 | ±2 | ±4 | ±2 | ±3 | ±5 | ±3 | ±4 |
| | | p = 0.01 | | p < 0.0001 | | p = 0.0007 | | p < 0.0001 |
| **T** | 38.5 | 38.7 | 38.7 | 38.7 | 38.7 | 38.5 | 38.6 | 38.1 |
| (°C) | ±0.3 | ±0.4 | ±0.3 | 0.2 | ±0.3 | ±0.2 | ±0.2 | ±0.2 |

Table 1: General hemodynamic results of nine pigs during 4 steps: pulmonary hypertension 25 mmHg ($PH_{25}$) and 40 mmHg ($PH_{40}$), cardiac output decrease ($CO_{down}$) and increase ($CO_{up}$). Values are presented as mean ± standard deviation. Modified Fick (FICK), Pulmonary artery (PATD) and transpulmonary thermodilution (TPTD), pulse contour analysis (PiCCO), continuous thermodilution (CCO), heart rate (HR), mean arterial blood pressure (MAP), central venous pressure (CVP), systemic vascular resistance (SVR = MAP-CVP * 80 / COFick), mean pulmonary arterial pressure (MPAP), pulmonary artery wedge pressure (PAWP),global ejection fraction (GEF = stroke volume / (global end-diastolic volume / 4)), Temperature (T). Statistical significance ($p<0.05$) between BL and step is marked with ⋆ and p values marked. The data was tested with paired t-tests.

Linear mixed model and Bland-Altman results (**Figures 2 a-d**) and percentage errors calculated for each step are presented in **Table 2**.

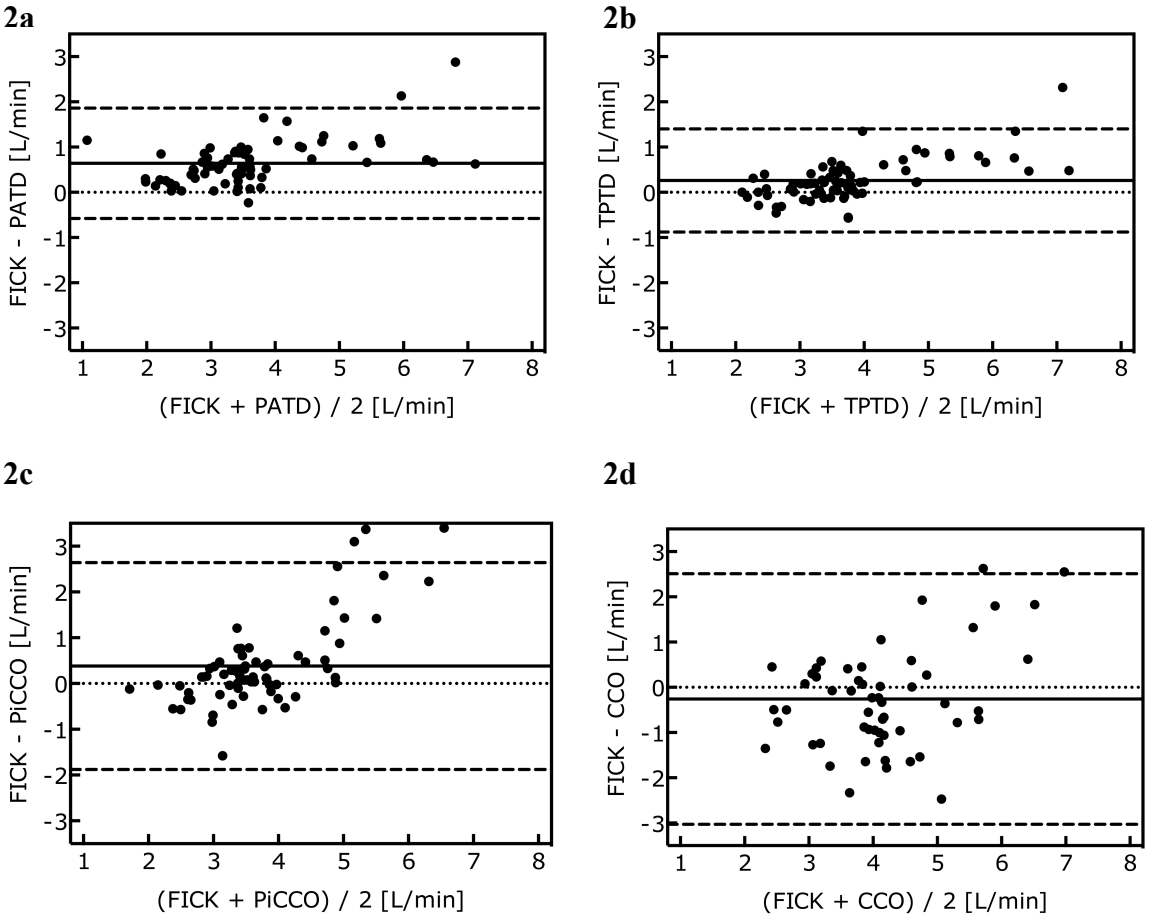



**Figure 2 Bland Altman plots for multiple comparisons per individual with the difference between the methods plotted against their mean**

a) FICK vs PATD
b) FICK vs TPTD
c) FICK vs PiCCO
d) FICK vs CCO

*Footnote:* FICK: modified Fick method, PATD: pulmonary artery thermodilution, TPTD: transpulmonary thermodilution, PiCCO: pulse contour analysis with PiCCOplus$^{TM}$, CCO: continuous thermodilution. The solid line represents the mean bias, the two broken lines the prediction intervals (bias ± 2.431 standard deviation); the dotted line is the line of equality.

**Table 2. Bland-Altman results**

| | Method 1 | Fick | | | | PATD | | | TPTD | | PiCCO |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Method 2 | PATD | TPTD | PiCCO | CCO | TPTD | PiCCO | CCO | PiCCO | CCO | CCO |
| All | n | 72 | 71 | 70 | 55 | 71 | 70 | 55 | 69 | 54 | 54 |
| | Mean bias (L/min) | 0.64 | 0.26 | 0.38 | -0.26 | -0.37 | -0.26 | -0.95 | 0.12 | -0.52 | -0.67 |
| | SD (L/min) | 0.50 | 0.47 | 0.93 | 1.14 | 0.23 | 0.73 | 0.87 | 0.69 | 0.93 | 0.83 |
| | Lower PI (L/min) | -0.58 | -0.88 | -1.88 | -3.03 | -0.93 | -2.03 | -3.06 | -1.56 | -2.78 | -2.69 |
| | Upper PI (L/min) | 1.86 | 1.40 | 2.64 | 2.51 | 0.19 | 1.51 | 1.16 | 1.80 | 1.74 | 1.35 |
| | Percentage error (%) | 34 | 30 | 61 | 67 | 16 | 52 | 55 | 46 | 56 | 51 |
| BL | n | 36 | 36 | 36 | 28 | 36 | 36 | 45 | 36 | 28 | 28 |
| | Mean bias (L/min) | 0.62 | 0.24 | 0.21 | -0.36 | -0.39 | -0.42 | -1.02 | -0.03 | -0.61 | -0.55 |
| | SD (L/min) | 0.39 | 0.35 | 0.38 | 0.76 | 0.19 | 0.37 | 0.62 | 0.35 | 0.74 | 0.76 |
| | Lower PI (L/min) | -0.33 | -0.61 | -0.71 | -2.21 | -0.85 | -1.32 | -2.53 | -0.88 | -2.41 | -2.40 |
| | Upper PI (L/min) | 1.57 | 1.09 | 1.13 | 1.49 | 0.07 | 0.48 | 0.49 | 0.82 | 1.19 | 1.30 |
| | Percentage error (%) | 27 | 23 | 25 | 44 | 14 | 26 | 40 | 23 | 45 | 45 |
| PH 25 | n | 9 | 9 | 9 | 7 | 9 | 9 | 7 | 9 | 7 | 7 |
| | Mean bias (L/min) | 0.65 | 0.87 | 0.35 | -0.51 | -0.47 | -0.31 | -1.24 | 0.16 | -0.69 | -0.86 |
| | SD (L/min) | 0.46 | 0.39 | 0.40 | 0.85 | 0.27 | 0.38 | 0.59 | 0.36 | 0.79 | 0.72 |
| | Lower PI (L/min) | -0.47 | -0.08 | -0.62 | -2.58 | -1.13 | -1.23 | -2.67 | -0.72 | -2.61 | -2.61 |
| | Upper PI (L/min) | 1.77 | 1.82 | 1.32 | 1.56 | 0.19 | 0.61 | 0.19 | 1.04 | 1.23 | 0.89 |
| | Percentage error (%) | 33 | 26 | 28 | 52 | 20 | 29 | 42 | 26 | 52 | 45 |
| PH 40 | n | 9 | 9 | 7 | 6 | 9 | 7 | 6 | 7 | 6 | 6 |
| | Mean bias (L/min) | 0.34 | 0.01 | 0.08 | -1.08 | -0.33 | -0.43 | -1.37 | -0.18 | -1.07 | -1.11 |
| | SD (L/min) | 0.27 | 0.32 | 0.50 | 0.75 | 0.22 | 0.32 | 0.78 | 0.27 | 0.97 | 0.90 |
| | Lower PI (L/min) | -0.32 | -0.77 | -1.14 | -2.90 | -0.86 | -1.21 | -3.27 | -0.84 | -3.43 | -3.30 |
| | Upper PI (L/min) | 1.00 | 0.79 | 1.30 | 0.74 | 0.20 | 0.35 | 0.53 | 0.48 | 1.29 | 1.08 |
| | Percentage error (%) | 22 | 25 | 37 | 53 | 18 | 25 | 53 | 20 | 64 | 62 |
| CO down | n | 9 | 8 | 9 | 7 | 8 | 9 | 7 | 8 | 6 | 7 |
| | Mean bias (L/min) | 0.40 | -0.01 | -0.48 | -1.07 | -0.32 | -0.88 | -1.51 | -0.51 | -1.01 | -0.76 |
| | SD (L/min) | 0.35 | 0.26 | 0.48 | 0.90 | 0.18 | 0.56 | 0.86 | 0.59 | 0.85 | 1.07 |
| | Lower PI (L/min) | -0.45 | -0.64 | -1.65 | -3.26 | -0.76 | -2.24 | -3.60 | -1.94 | -3.08 | -3.36 |
| | Upper PI (L/min) | 1.25 | 0.62 | 0.69 | 1.12 | 0.12 | 0.48 | 0.58 | 0.92 | 1.06 | 1.84 |
| | Percentage error (%) | 41 | 27 | 46 | 78 | 20 | 59 | 86 | 55 | 71 | 87 |
| CO up | n | 9 | 9 | 9 | 7 | 9 | 9 | 7 | 9 | 7 | 7 |
| | Mean bias (L/min) | 1.22 | 0.94 | 2.41 | 1.81 | -0.28 | 1.19 | 0.49 | 1.46 | 0.84 | -0.66 |
| | SD (L/min) | 0.78 | 0.58 | 0.77 | 0.69 | 0.31 | 0.70 | 0.61 | 0.61 | 0.60 | 0.92 |
| | Lower PI (L/min) | -0.68 | -0.47 | 0.54 | 0.13 | -1.03 | -0.51 | -0.99 | -0.02 | -0.62 | -2.90 |
| | Upper PI (L/min) | 3.12 | 2.35 | 4.28 | 3.49 | 0.47 | 2.89 | 1.97 | 2.94 | 2.30 | 1.58 |
| | Percentage error (%) | 31 | 23 | 34 | 28 | 13 | 35 | 30 | 30 | 28 | 47 |

Bland-Altman cardiac output (CO) results for multiple measurements per subject of 9 pigs measured with Modified Fick (FICK), pulmonary artery (PATD) and transpulmonary thermodilution (TPTD), pulse contour analysis (PiCCO) and continuous thermodilution (CCO).

All: all measurements pooled, BL: all baselines pooled, PH 25 and PH 40: pulmonary hypertension 25 mmHg and 40 mmHg, $CO_{down}$: CO decrease and $CO_{up}$ : CO increase.Values are presented as mean bias, SD: standard deviation, lower and upper PI: 95% prediction intervals (= mean bias ± 2.431 SD), percentage error = 100 x 2.431 x SD / mean CO of both methods.

The TPTD bolus method showed good trending ability compared to FICK and PATD with a concordance rate of 100% with 95% CI of 94 to 100%. The concordance rate of PATD against FICK was 96% (87-100%). Both continuous methods showed limited trending abilities with concordance rates below 90% (**Table 3** and **Figures 3a-d**).

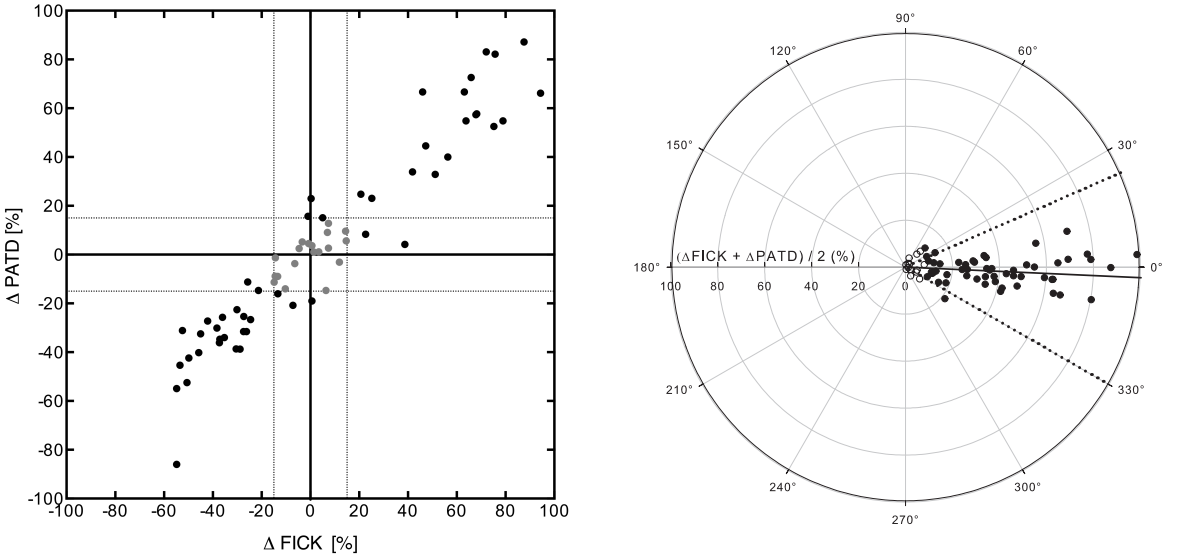
**Table 3 Trending results**

| Method 1 | FICK | | | | PATD | | | TPTD | | PiCCO |
|---|---|---|---|---|---|---|---|---|---|---|
| Method 2 | PATD | TPTD | PiCCO | CCO | TPTD | PiCCO | CCO | PiCCO | CCO | CCO |
| Exclusion zone ≤15% | | | | | | | | | | |
| Data points | 71 | 70 | 67 | 54 | 70 | 66 | 54 | 66 | 52 | 52 |
| > 15 % change | 52 | 50 | 45 | 42 | 50 | 50 | 42 | 49 | 40 | 39 |
| Wrong quarter | 2 | 0 | 7 | 5 | 0 | 7 | 5 | 7 | 6 | 6 |
| Concordance rate | 96% | 100% | 84% | 88% | 100% | 86% | 88% | 86% | 85% | 85% |
| Confidence interval (%) | *87-100% | *93-100% | 71-92% | 74-95% | *94-100% | 69-94% | 67-98% | 69-94% | 65-96% | 70-93% |
| Exclusion zone ≤10% | | | | | | | | | | |
| Mean polar angle | -2° | -3° | -17° | -19° | -1° | -19° | -17° | -14° | -15° | -2° |
| Standard deviation | 14° | 11° | 22° | 22° | 8° | 25° | 19° | 25° | 20° | 27° |
| Radial limits of agreement | 28° | 28° | 45° | 40° | 16° | 50° | 30° | 48° | 41° | 43° |

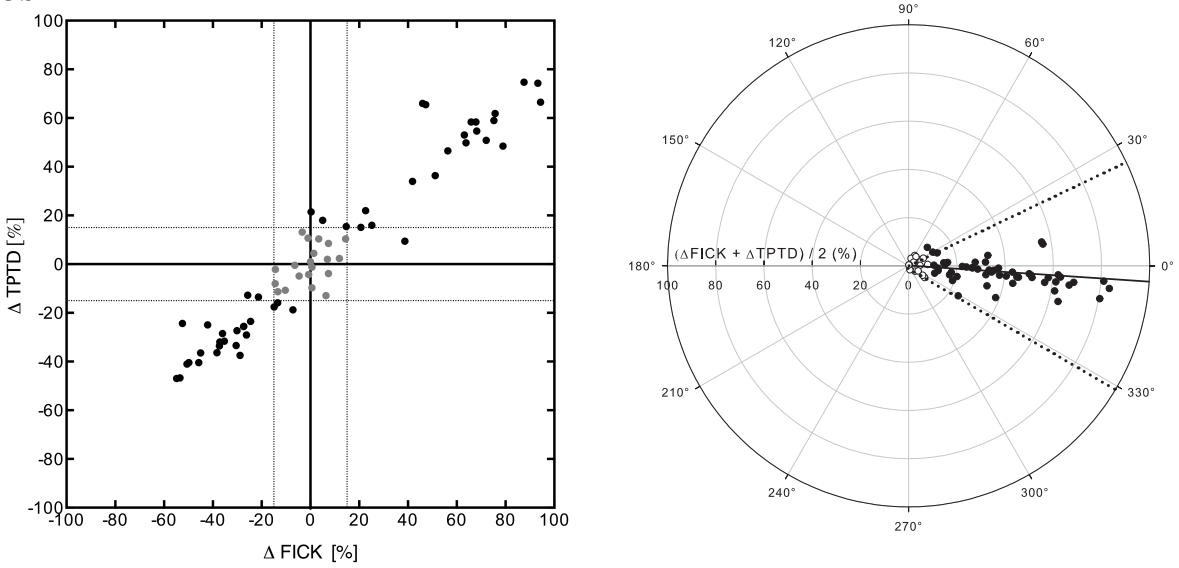
Concordance and polar plot results of 9 pigs measured with modified Fick (FICK), pulmonary artery (PATD) and transpulmonary thermodilution (TPTD), pulse contour analysis (PiCCO) and continuous thermodilution (CCO). Exclusion zones were set at ≤10 (polar plot) and ≤15% (concordance) change of CO.

Values are presented as concordance rate (> 15% change – wrong quarter) / > 15% change with 95% confidence intervals (*due to non-convergence of the models, binomial confidence intervals are presented), mean polar angle, standard deviation and radial limits of agreement (95% of data points).

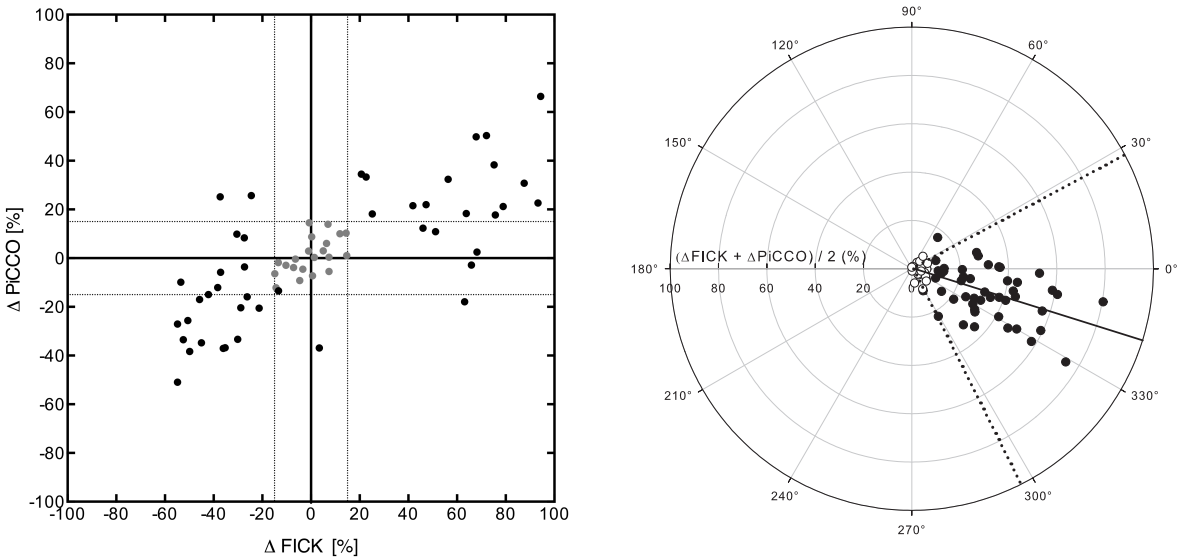
**3a**


Δ PATD [%]
Δ FICK [%]
(ΔFICK + ΔPATD) / 2 (%)

**3b**


Δ TPTD [%]
Δ FICK [%]
(ΔFICK + ΔTPTD) / 2 (%)

**3c**


Δ PiCCO [%]
Δ FICK [%]
(ΔFICK + ΔPiCCO) / 2 (%)

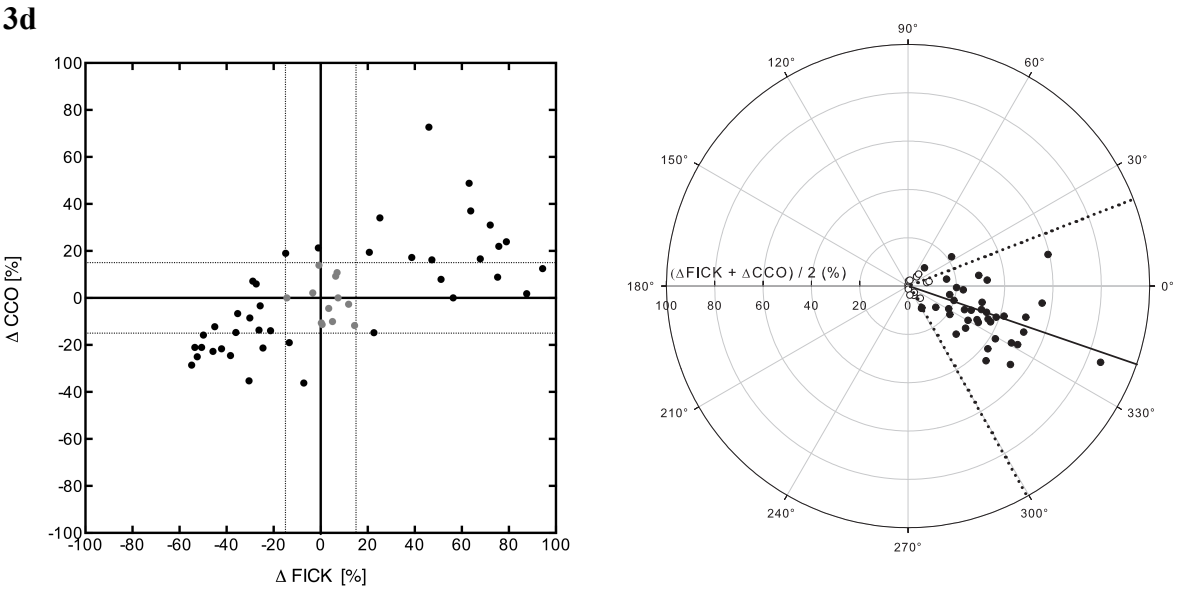



**Figure 3 Concordance and polar plots of percentage change that compare trending abilities between 5 methods of cardiac output measurement**

a) FICK vs PATD
b) FICK vs TPTD
c) FICK vs PiCCO
d) FICK vs CCO

*Footnote:* FICK: modified Fick method, PATD: pulmonary artery thermodilution, TPTD: transpulmonary thermodilution, PiCCO: pulse contour analysis with PiCCOplus$^{TM}$, CCO: continuous thermodilution.
In the concordance plot the dotted lines limit an exclusion zone of 15%. Values within this zone are shown in grey. Black dots in the left upper and right lower quadrant but outside of the central grey 15% zone are signs for inadequate trending of CO changes.
Half circle polar plots are shown with data transformed to positive directional data only, the distance from the center represents the mean change in cardiac output (ΔCO) and the angle θ with the horizontal axis depicts the agreement of the methods. Data points outside a 30° from the 0° horizontal axis are a sign for inadequate trending. Data points with mean changes ≤ 10% were excluded from the analysis and are shown as open circles. Solid line: mean polar angle; dotted lines: radial limits of agreement.

Mean pulmonary artery blood pressure did influence the difference between FICK and PiCCO measurements as assessed by linear mixed effects models. The differences between FICK and PATD, TPTD and CCO respectively were not influenced by mean pulmonary artery blood pressure. Both mean arterial and mean pulmonary artery blood pressure, were influenced by the steps (interaction effect between mean arterial and mean pulmonary artery blood pressure and steps). Based on Akaike information criteria, there was no evidence that the triplicate measurements with PATD and TPTD differed in their variability.

## Discussion

In this study the influence of two degrees of acute PH and CO de- and increases on the accuracy and the trending ability of four CO methods compared to FICK were assessed in nine pigs. Both intermittent methods TPTD and PATD yielded good trending ability

compared to FICK. The bolus method TPTD showed better agreement than PATD with FICK CO measurements. Both continuous CO measurement methods - PiCCO and CCO - showed poor accuracy and limited trending ability as compared with FICK. No influence of pulmonary artery pressure on the difference between all thermodilution methods PATD, TPTD and CCO was revealed by linear mixed models. Only the difference between FICK and the pulse contour analysis PiCCO was influenced by pulmonary artery pressure.

The results of this study regarding TPTD are in agreement with a variety of other studies evaluating the performance of TPTD. These previous studies assessed CO by TPTD against PATD under different clinical conditions but none of them involved PH. Based on the present favorable results it can be argued that TPTD can reliably be used for CO measurements as an alternative to PATD avoiding a pulmonary artery catheter. Although adequate accuracy of CO measurement by thermodilution techniques in PH patients[23] or animal models of tricuspid regurgitation have been reported,[24] it has - unfortunately - to be emphasized that thermodilution may under- or overestimate CO due to inadequate mixing or loss of indicator when PH and tricuspid regurgitation develop.[7, 25] Therefore, the Fick method has still to be considered the standard of CO measurement under these specific clinical conditions.[4] The current data suggests better agreement and trending ability of TPTD than of PATD when compared to FICK. Considering technical aspects of these techniques, PATD (measurement in the right heart) may be more influenced than TPTD (measurement of the total vascular bed from right atrium to the left ventricular outflow) by changing pulmonary pressures.

All pulse contour methods have been shown to be susceptible to changes in peripheral vascular resistance.[13,26-28] The calibrated methods have the advantage that they can be recalibrated in order to better reflect any acute changes of vascular tone. The present study protocol involved major induction of hemodynamic changes and vasoactive drug application. As a result inferior agreement of PiCCO and FICK measurements was observed despite recalibration before any next hemodynamic change was performed. Still, other studies observed a comparable PiCCO performance without the influence of PH.[11] The trending ability of PiCCO against FICK with concordance rates between 80% and 90% and polar plot results (radial limits of agreement of 45°) confirm these results. However, the applied linear mixed models did reveal an influence of mean pulmonary artery pressure on the difference between PiCCO and FICK measurements, opposed to no influence on all thermodilution measurement. This finding is unexpected and cannot be explained with the other findings of the current study. The device may still be used in its' continuous mode when elevated

pulmonary artery pressures are present, considering the requirement of frequent recalibration in order to guarantee acceptable CO measurement results under unstable hemodynamic conditions.[13,27]

The PiCCO system combining TPTD and the pulse contour method PiCCO allows the additional assessment of different volumetric and functional hemodynamic parameters. These parameters may help to early detect hemodynamic instability and to initiate prompt and appropriate hemodynamic therapy. During PH the right ventricle is dilated and can eject less flow through the lung vessels to the left ventricle. This seems to be correctly reflected by TPTD, as the left ventricle cannot deliver more flow than it receives from the right side. The concept 'pulmonary flow equals systemic flow' applies in this setting even if acute increases in mean pulmonary artery pressure may influence the cardiac work of the ventricles differently. If a PH patient is monitored with TPTD and PiCCO no direct measurements of pulmonary artery pressures are possible. As the severity of PH does not predict mortality,[4] it may be more important to correctly monitor cardiac function than measure exact pulmonary artery pressures with a pulmonary artery catheter. Echocardiography can be used to intermittently estimate pressures and assess the function of both ventricles.

In the present study comparing CCO to FICK resulted in low agreement and a limited trending ability. In this acute setting CCO updates were apparently too slow to reliably track changes.[12] In order to detect changes appropriately, the changes induced during and after the different hemodynamic steps would have to be stable for at least 10 to 20 minutes before each comparative hemodynamic assessment. High CCO values measured may be the result of a catheter-related problem. Clearly, the positions of the pulmonary artery catheter proximal and distal openings' were verified using the detection of the typical pressure waveforms and the related changes during insertion. Still, the length of the heating wire might have been too long for these pigs that had a weight of 26 kg. However, linear mixed models indicate that PH does not influence the difference between CCO and FICK, and CCO measurements can probably be used in PH patients to monitor CO at the bedside considering a delay of up to 10 minutes[12] and the typical limitations of thermodilution methods under PH.

Major limitations of the present study are primarily related to the animal model and the measurement techniques used during PH:

Pharmacologically induced hypertension in animals with normal pulmonary vessels was used as a model for a variance of pathophysiological different diseases causing PH.[29] Typically around 50% of the possible increase of pulmonary vascular resistance in PH patients is

mediated through reversible vasoconstriction,[4] although individual variations of vascular involvement might be observed. Moreover, our model is not able to mimic vascular remodeling, thrombosis or congestion from the left atrium. It can only reflect pulmonary arterial hypertension with low left atrial pressure, i.e. the so-called pre-capillary PH.[29] Therefore, no conclusion regarding CO measurement performance in patients with different classes of PH having vascular remodeling or left ventricular impairment as result of a failing right heart can be made.

Two bolus methods were assessed by analyzing the temperature changes induced by the same bolus of ice-cold fluid, a technique that should reduce the influence of temporal changes of CO and therefore decrease type I errors between the methods. Recalibration of PiCCO before each subsequent measurement period may also have reduced the error compared to longer calibration free periods. Another source of error may be the intravenous administration of 30 mL/kg Ringers lactate in order to increase CO in a randomized order. Moreover, the comparison of a less invasive method with a reference method requiring a pulmonary artery catheter possibly increased tricuspid regurgitation along the catheter, which may lead to a further loss of indicator in the thermodilution methods. To avoid this, TPTD may be compared to a CO measurement method such as Doppler flow measurement. However, the placement of a flow probe around the pulmonary artery requires a thoracotomy, which was avoided in these animals due to concurrent studies.

Fick measurement was chosen as the reference method to exclude a potential influence of PH or tricuspid regurgitation. We did not measure oxygen consumption during the study and therefore had to use a modified Fick method. We divided the measured $CO_2$ production by a respiratory quotient of 0.8 to receive $O_2$ consumption. This estimated respiratory quotient may have introduced a source of error that cannot be quantified in the current study.

In the current study presence of tricuspid regurgitation or other valvular abnormalities was not quantified by transesophageal echocardiography.

Our data suggests good trending ability of TPTD and PATD compared to FICK. TPTD yielded better results of agreement than PATD with FICK CO measurements. The trending abilities of the PiCCO and CCO were limited and when used clinically in unstable patients, regular controls with intermittent techniques are required. Acute pharmacologically induced PH did influence the difference between Fick and PiCCO.

## Acknowledgements

This study was supported by Axon Lab Switzerland and funded by a grant from the Forschungskredit of the University of Zurich.

## References

1. Reich DL, Bodian CA, Krol M, Kuroda M, Osinski T, Thys DM. Intraoperative hemodynamic predictors of mortality, stroke, and myocardial infarction after coronary artery bypass surgery. Anesth Analg 1999;89:814-22
2. Kaw R, Pasupuleti V, Deshpande A, Hamieh T, Walker E, Minai OA. Pulmonary hypertension: an important predictor of outcomes in patients undergoing non-cardiac surgery. Respir Med 2011;105:619-24
3. Lai HC, Wang KY, Lee WL, Ting CT, Liu TJ. Severe pulmonary hypertension complicates postoperative outcome of non-cardiac surgery. Br J Anaesth 2007;99:184-90
4. Chemla D, Castelain V, Herve P, Lecarpentier Y, Brimioulle S. Haemodynamic evaluation of pulmonary hypertension. Eur Resp J 2002;20:1314-33
5. Harvey S, Harrison DA, Singer M, Ashcroft J, Jones CM, Elbourne D, Brampton W, Williams D, Young D, Rowan K. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. Lancet 2005;366:472-7
6. Hoeper MM, Lee SH, Voswinckel R, Palazzini M, Jais X, Marinelli A, Barst RJ, Ghofrani HA, Jing ZC, Opitz C, Seyfarth HJ, Halank M, McLaughlin V, Oudiz RJ, Ewert R, Wilkens H, Kluge S, Bremer HC, Baroke E, Rubin LJ. Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. J Am Coll Cardiol 2006;48:2546-52
7. Heerdt PM, Blessios GA, Beach ML, Hogue CW. Flow dependency of error in thermodilution measurement of cardiac output during acute tricuspid regurgitation. J Cardiothor Vasc Anesth 2001;15:183-7
8. Orme RM, Pigott DW, Mihm FG. Measurement of cardiac output by transpulmonary arterial thermodilution using a long radial artery catheter. A comparison with intermittent pulmonary artery thermodilution. Anaesthesia 2004; 59:590-4
9. Hartnack S. Issues and pitfalls in method comparison studies. Vet Anaesth Analg 2014; 41:227-32
10. Critchley LA, Lee A, Ho AM-H. A critical review of the ability of continuous cardiac output monitors to measure trends in cardiac output. Anesth Analg 2010;111:1180-92

11. Critchley LA, Yang XX, Lee A. Assessment of trending ability of cardiac output monitors by polar plot methodology. J Cardiothor Vasc Anesth 2011;25:536-46
12. Poli de Figueiredo LF, Malbouisson LM, Varicoda EY, Carmona MJ, Auler JO, Jr., Rocha e Silva M. Thermal filament continuous thermodilution cardiac output delayed response limits its value during acute hemodynamic instability. J Traum 1999;47:288-93
13. Piehl MD, Manning JE, McCurdy SL, Rhue TS, Kocis KC, Cairns CB, Cairns BA. Pulse contour cardiac output analysis in a piglet model of severe hemorrhagic shock. Crit Care Med 2008;36:1189-95.
14. Axiak Flammer SM, Critchley LA, Weber A, Pirbodaghi T, Brinks H, Vandenberghe S. Reliability of lithium dilution cardiac output in anaesthetized sheep. Br J Anaesth 2013;111:833-9.
15. Martin-Cancho MF, Carrasco-Jimenez MS, Lima JR, Ezquerra LJ, Crisostomo V, Uson-Gargallo J. Assessment of the relationship of bispectral index values, hemodynamic changes, and recovery times associated with sevoflurane or propofol anesthesia in pigs. Am J Vet Res 2004;65:409-16
16. Mosing M, Kutter APN, Iff S, Raszplewicz J, Mauch J, Bohm SH, Tusman G. The effects of cardiac output and pulmonary arterial hypertension on volumetric capnography derived-variables during normoxia and hypoxia. J Clin Monit Comput 2014; doi 10.1007/s10877-014-9588-0
17. Combes A, Berneau JB, Luyt CE, Trouillet JL. Estimation of left ventricular systolic function by single transpulmonary thermodilution. Intens Care Med 2004; 30: 1377-83
18. Critchley LA, Critchley JA. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. J Clin Monit Comput 1999;15:85-91
19. Akaike H. A new look at the statistical model identification. Automatic Control, IEEE Transactions on 1974; 19: 716-23
20. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing 2014, http://www.R-project.org/
21. Pinheiro J, Bates B, DepRoy S, Sarkar D, R Core Team. nlme: Linear and nonlinear mixed effects models. 2014, http://CRAN.R-project.org/package=nlme
22. Carstensen B, Gurrin L, Ekstrom C, Figurski M. MethComp: Functions for analysis of agreement in method comparison studies. 2013, http://CRAN.R-project.org/package=MethComp

23. Hoeper M, Maier R, Tongers J, Niedermeyer J, Hohlfeld J, Hamm M, Fabel H. Determination of cardiac output by the Fick method, thermodilution, and acetylene rebreathing in pulmonary hypertension. Am J Resp Crit Care 1999;160:535-41
24. Buffington CW, Nystrom EU. Neither the accuracy nor the precision of thermal dilution cardiac output measurements is altered by acute tricuspid regurgitation in pigs. Anesth Analg 2004;98:884-90
25. Nishikawa T, Dohi S. Errors in the measurement of cardiac output by thermodilution. Can J Anaesth 1993;40:142-53
26. Hadian M, Kim HK, Severyn DA, Pinsky MR. Cross-comparison of cardiac output trending accuracy of LiDCO, PiCCO, FloTrac and pulmonary artery catheters. Crit Care 2010;14:R212
27. Bein B, Meybohm P, Cavus E, Renner J, Tonner P, Steinfath M, Scholz J, Doerges V. The reliability of pulse contour-derived cardiac output during hemorrhage and after vasopressor administration. Anesth Analg 2007;105:107-13
28. Bektas RN, Kutter APN, Hartnack S, Jud RS, Schnyder M, Matos JM, Bettschart-Wolfensberger R. Evaluation of a minimally invasive non-calibrated pulse contour cardiac output monitor (FloTrac/Vigileo) in anaesthetized dogs. Vet Anaesth Analg 2012;39:464-71
29. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, Langleben D, Manes A, Satoh T, Torres F, Wilkins MR, Badesch DB. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 2013;62:D42-50